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Effects of escitalopram/quetiapine combination therapy versus escitalopram monotherapy on hypothalamic–pituitary–adrenal-axis activity in relation to antidepressant effectiveness

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ABSTRACT

The hypothalamic–pituitary–adrenocortical (HPA) system is believed to play an important role in the pathophysiology of major depressive disorder. In this context, the atypical antipsychotic quetiapine (QUE) has been shown to inhibit HPA system activity in healthy subjects. In this study we investigated whether the putative inhibitory effects of QUE on HPA system activity may contribute to its antidepressant efficacy. We analyzed the effects of QUE as an augmentation to the selective serotonin reuptake inhibitor (SSRI) escitalopram (ESC) on HPA system activity in comparison to a monotherapy with ESC in relation to the antidepressant effectiveness. HPA axis activity (cortisol and ACTH) was measured by means of the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test which was performed before (week 0) and during (week 1, week 5) antidepressant psychopharmacotherapy. The combination therapy, but not the ESC monotherapy showed significantly inhibiting effects on HPA system activity leading to stepwise down-regulation. ACTH concentrations were reduced in the ESC/QUE group during five weeks of treatment. The inhibitory effect of QUE maybe involved in its antidepressant effects as an augmentation strategy.

1. Introduction

Depression is a very frequent and highly disabling disorder which is of high socioeconomic impact. This disorder is suggested to rank first regarding burden of disease within the next two decades (Mathers and Loncar, 2006). The etiology of depression is manifold, genetic as well as psychosocial factors are supposed to be involved. Regarding neurobiological sources of depression, a dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) system in terms of hyperactivity has been shown repeatedly (Holsboer, 2000; Miller et al., 2007; Schule et al., 2009b). Pathophysiologically, a disturbed feedback mechanism within the HPA system involving altered glucocorticoid receptor sensitivity and a hypersecretion of corticotropin-releasing hormone (CRH) and arginine–vasopressin (AVP) leads to elevated levels of adrenocorticotropic hormone (ACTH) and cortisol (Barden, 2004; Hatzinger et al., 2004; Nikisch, 2009). From a therapeutic point of view, the normalization of this HPA system dysregulation might play a key role for successful antidepressive treatment (Holsboer, 2000; Holsboer and Ising, 2010; Schule et al., 2009a,b).

Regarding pharmacological antidepressive therapy, selective serotonin reuptake inhibitors (SSRIs) such as citalopram are considered as first class treatment options (Gelenberg, 2010). Regarding HPA system activity, initial hyperactivation is downregulated to normal levels by citalopram in depressed patients (Nikisch et al., 2005, 2008). More recently, the S-enantiomer of this compound (escitalopram, ESC) has been introduced into the market because this isoform is supposed to basically mediate antidepressant efficacy, maybe due to its higher binding affinity to the serotonin transporter (Owens et al., 2001).

Quetiapine (QUE) is an atypical antipsychotic which has also been successfully applied as an antidepressive compound (Komossa et al., 2010). It reveals antidepressant efficacy as a monotherapy in major depressive disorder and bipolar depression (Calabrese et al., 2005; McIntyre et al., 2009; Weisler et al., 2009). In clinical practice, this compound is licensed as an augmentation

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strategy in unipolar depression if the antidepressant efficacy of e.g. SSRIs is not sufficient (Philip et al., 2008; Shelton and Papakostas, 2008). In bipolar disorder, QUE is approved as a monotherapy (Bogart and Chavez, 2009). Pharmacologically, QUE antagonizes dopamine D_1, D_2 (with lower affinity), adrenergic $\alpha 1$, histaminergic H_1 and serotonergic 5-HT_2 receptors (Fountoulakis et al., 2011). Moreover, QUE inhibits acute hypothalamic CRH release by blocking 5-HT_2 and H_1 receptors (Cohrs et al., 2006; de Borja Goncalves et al., 2005).

The aim of this open-label, non-randomized study was to investigate the endocrine effects of a combination therapy with ESC/QUE compared to ESC monotherapy on HPA system activity. Furthermore, we analyzed whether putative changes correlate with depressive symptom reduction. Both treatment strategies were expected to be effective. Moreover, it was assumed that QUE might have a further beneficial effect in addition to ESC. With regard to HPA system activity, both therapies were expected to down-regulate the system according to the corticosteroid hypothesis of depression (Holsboer, 2000).

2. Subjects and methods

2.1. Study subjects

40 unrelated in-patients (21 men and 19 women, mean age 44.40 ± 12.22 years) suffering from a major depressive episode according to DSM-IV criteria (296.2 or 296.3) were investigated. See Table 1 for details of clinical and demographical characteristics of depressed patients at admission. Patients with major neurological or other medical disorders, addiction, or other comorbid psychiatric disorders or suicidality were not included into the study. For female patients pregnancy had to be excluded. Furthermore, normal laboratory parameters, blood pressure, electrocardiogram and encephalogram were required. Moreover, no psychotropic drugs for at least 3 days before the first DEX/CRH test (see below) with the exception of zopiclone (up to 7.5 mg per day) in case of sleep difficulties and lorazepam (up to 2 mg per day) in case of inner tension and anxiety were allowed. Patients had a Hamilton (1960) depression rating scale sum score of at least 18 on the 21-item version (HAMD-21). The ratings were performed by experienced psychiatrists who were blind to hormonal measurements. Written informed consent was obtained from all patients after a detailed and extensive description of the study. Patients did not receive payment or other rewards for study participation. During the study, one patient of the ESC/QUE combination therapy group dropped out due to premature discharge against medical advice. The study was carried out according to the Declaration of Helsinki (http://www.wma.net) and had been approved both by a local ethics committee (intramural review panel of the Ludwig-Maximilians-University of Munich, Faculty of Medicine) and the Federal Institute for Drugs and Medical Devices in Germany.

2.2. Study design

In this open-label, non-randomized study patients were assigned to one of the following two treatment arms according to clinical judgment at the discretion of the psychiatrist in attendance: escitalopram (ESC) monotherapy 10–20 mg per day or a combination therapy of escitalopram 10–20 mg and quetiapine 200 mg per day (ESC/QUE). With regard to the allocation to the treatment groups, clinical criteria such as loss of energy, inner tension, or sleep difficulties played an important role. To assess the baseline neuroendocrine status, a first DEX/CRH test (week 0) was carried out after a drug-free period of at least three days within the first week after admission to hospital. Briefly, an oral dose of 1.5 mg DEX was given to the patients at 23:00 the evening prior to the test. On the following day, the patients received an intravenous catheter before 14:15 and were requested to calmly rest on a bed for the time of testing. Blood samples were collected at 15:00, 15:15, 15:30, 15:45, 16:00 and 16:15. All samples were immediately centrifuged and stored at −80 °C. At 15:02 100 μg CRH (Clinalfa AG, Läufelfingen, Switzerland) dissolved in 0.2% HCl/0.9% saline were rapidly injected. Cortisol and ACTH serum levels were determined by a commercial electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. The detection limit for cortisol was 0.500 nmol/l and 0.220 pmol/l for ACTH. The day after the first DEX/CRH test, patients received antidepressant medication according to

Table 1
Characteristics of depressive patients at admission. Data represent mean ± SEM (standard error of the mean). ESC = escitalopram; QUE = quetiapine; MAP = mean arterial blood pressure; bpm = beats per minute; HAMD-21 = Hamilton depression rating scale, 21-item version. Clinical response (responder) was defined by a reduction of at least 50% of the HAMD-21 score after five weeks of treatment. Remitters were defined as a HAMD-21 score of less than eight after the five weeks treatment.

	All patients	Male	Female	ESC/QUE	ESC
Number	40	21	19	20	20
Age (years)	44.40 ± 1.93	44.52 ± 2.47	44.26 ± 3.09	46.75 ± 2.68	42.05 ± 2.75
Height (cm)	171.71 ± 1.12	175.95 ± 0.96	167.47 ± 1.52	169.50 ± 1.52	1.73.70 ± 1.50
Weight (kg)	71.84 ± 1.98	79.37 ± 2.12	64.32 ± 2.38	71.80 ± 3.05	71.88 ± 2.63
Cigarettes/day	4.09 ± 1.46	3.90 ± 1.59	4.21 ± 2.57	2.75 ± 2.10	5.35 ± 2.04
MAP (mmHg)	127.08 ± 2.34/ 78.65 ± 1.82	132.71 ± 2.65/ 82.33 ± 2.39	120.84 ± 3.48/ 74.58 ± 2.51	125.95 ± 3.45/ 77.45 ± 2.98	128.20 ± 3.22/ 79.85 ± 2.13
Heart rate (bpm)	80.05 ± 2.27	76.29 ± 2.46	84.21 ± 3.77	80.95 ± 3.33	79.15 ± 3.16
Responder	27	16	11	12	15
Remitter	14	11	3	4	10
Non-responder	13	5	8	8	5
HAMD-21 sum score week 0	28.20 ± 0.98	28.38 ± 1.52	28.00 ± 1.22	30.45 ± 1.50	25.95 ± 1.06
Duration of current depressive episode (weeks)	18.84 ± 5.08	14.09 ± 2.81	24.10 ± 10.26	24.49 ± 9.74	13.34 ± 2.80
Number of depressive episodes	2.15 ± 0.21	1.95 ± 0.27	2.37 ± 0.33	2.55 ± 0.35	1.75 ± 0.20
Duration since onset of disease (months)	109.12 ± 22.18	69.24 ± 20.07	153.22 ± 39.30	145.37 ± 37.51	72.89 ± 21.81
Duration of current admission (weeks)	10.21 ± 1.91	8.37 ± 1.37	12.25 ± 3.73	10.70 ± 1.71	9.72 ± 3.47